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Acknowledging differences in Acute Kidney Injury

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Chapter2

INCIDENCE, TIMING AND OUTCOME OF AKI IN CRITICALLY ILL PATIENTS VARIES WITH THE DEFINITION USED AND THE ADDITION OF URINE OUTPUT CRITERIA

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Abstract

Background

Acute kidney injury (AKI) is a serious complication of critical illness with both attributed morbidity and mortality at short-term and long-term. The incidence of AKI reported in critically ill patients varies substantially with the population evaluated and the definitions used. We aimed to assess which of the AKI definitions (RIFLE, AKIN or KDIGO) with or without urine output criteria recognizes AKI most frequently and quickest. Additionally, we conducted a review on the comparison of incidence proportions of varying AKI definitions in populations of critically ill patients.

Methods

We included all patients with index admissions to our intensive care unit (ICU) from January 1st, 2014 until June 11th, 2014 to determine the incidence and onset of AKI by RIFLE, AKIN and KDIGO during the first 7 days of ICU admission. We conducted a sensitive search using PubMed evaluating the comparison of RIFLE, AKIN and KDIGO in critically ill patients.

Results

AKI incidence proportions were 15, 21 and 20% respectively using serum creatinine criteria of RIFLE, AKIN and KDIGO. Adding urine output criteria increased AKI incidence proportions to 35, 38 and 38% using RIFLE, AKIN and KDIGO definitions. Urine output criteria detected AKI in patients without AKI at ICU admission in a median of 13 hours (IQR 7-22 hours; using RIFLE definition) after admission compared to a median of 24 hours using serum creatinine criteria (IQR 24-48 hours). In the literature a large heterogeneity exists in patients included, AKI definition used, reference or baseline serum creatinine used, and whether urine output in the staging of AKI is used.

Conclusion

AKIN and KDIGO criteria detect more patients with AKI compared to RIFLE criteria. Addition of urine output criteria detect patients with AKI 11 hours earlier than serum creatinine criteria and may double AKI incidences in critically ill patients. This could explain the large heterogeneity observed in literature.

Keywords

Acute Kidney Injury, Definitions, Incidence, Intensive Care, Timing

Summary

The AKI definition which is used and whether serum creatinine is combined with urine output criteria determines the AKI incidence and the AKI outcome. Adding urine output criteria detects AKI quicker than using only serum creatinine.

Background

Acute kidney injury (AKI) is a serious complication of critical illness with both attributed morbidity and mortality at short and long-term [1-7]. The incidence of AKI reported in critically ill patients varies substantially [4, 8]. Before 2004 the diagnosis of AKI was based on urine output and markers of decreased urinary waste secretion i.e., serum urea and creatinine as markers of a decreased glomerular filtration rate (GFR), but differed per study. In 2004 an attempt was made to standardize outcomes of studies by unifying the definition of AKI using the Risk, Injury, Failure, Loss and End-stage (RIFLE) definitions [9]. In 2007 adjustments resulted in the Acute Kidney Injury Network (AKIN) definition, driven by observations that minor increases in serum creatinine over a shorter time period are also associated with adverse effects. The current definition made by Kidney Disease Improving Global Outcomes (KDIGO) is similar to the AKIN definition but the time frame is extended from 48 hours to 7 days [10, 11]. Serum creatinine is considered an inferior marker of kidney function during critical illness, as the rise in serum creatinine is commonly delayed after kidney function decline [12, 13]. Adding urine output criteria to creatinine levels increases AKI incidences compared to criteria using serum creatinine levels only [14-18]. However, many studies dismiss hourly urine output data as this data is often hampered by frequent missing values. Consequently, studies may report AKI using three different definitions, all with or without urine output criteria. Comparison of published studies is hampered by this dissimilarity.

Objective

We aimed to assess the difference in AKI incidence using the three definitions, with and without urine output criteria, and to assess which AKI definition recognizes AKI first. Second, we aimed to assess differences in patient characteristics in patients with AKI according to the three definitions. Additionally, we conducted a review on incidence proportions of AKI varying with definitions in critically ill patients.

Methods

I. Cohort study

We included all patients with index admissions to our intensive care unit (ICU) from January 1st, 2014 until June 11th, 2014. Informed consent was waived by the institutional Review Board of our hospital because the study had an observational design and all data were de-identified (METc University Medical Center Groningen, Medical Ethical Committee, reference number 2013-174).

Data collection

Baseline data were recorded for all patients, including age, sex, Body Mass Index (BMI), admission category and type (medical and surgical; scheduled and emergency), the presence of diabetes mellitus, and chronic kidney disease. We recorded mortality and length of stay (ICU and hospital). Serum creatinine was measured each day and urinary output was recorded hourly. Reference creatinine was based on the calculated ideal serum creatinine assuming a clearance of 75 ml/

min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) formula. Missing hourly urine output data was imputed based on averages using the first known value over the missing hours. AKI timing and incidence was estimated up to the first seven ICU admission days.

Definitions of AKI

AKI during the first 7 days of ICU admission was defined according to the RIFLE, AKIN and KDIGO definitions. Using serum creatinine with and without urine output criteria. The definitions are described in supplementary table 1.

Comparison of AKI definitions

RIFLE uses Glomerular Filtration Rate (GFR) criteria in addition to serum creatinine and urine output criteria. GFR criteria were abandoned in the AKIN and KDIGO definitions. The Risk, Injury and Failure categories of the RIFLE definition were replaced by AKIN and KDIGO stages 1, 2 and 3. In AKIN stage 1 an absolute rise in serum creatinine of more than 26.4 µmol/l was added to the relative increase of 150-200% in serum creatinine compared to baseline. This increase in serum creatinine of more than 26.4 µmol/l in AKIN stage 1 was replaced by an absolute rise in serum creatinine of more than 26.5 µmol/l in stage 1 of the KDIGO definition. Both in the RIFLE and KDIGO definitions the increase in creatinine is defined to occur within 7 days, which contrasts with the 48 hours used in the AKIN definition.

In stage 3 of the AKIN and KDIGO definitions the need for renal replacement therapy (RRT) was added. The categories Loss and End Stage Kidney disease or equivalent (outcome) categories from the RIFLE definition were removed from the AKIN and KDIGO definitions. Urine output criteria are similar in RIFLE, AKIN and KDIGO definitions.

Statistical analyses

Incidence proportions of AKI were based on definitions of AKI criteria during the first week of ICU admission. Baseline characteristics were reported by proportions and means (with standard deviations) or medians (with inter quartile ranges) according to normality or skewed distributions. Normality was tested using the Kolmogorov-Smirnov test. Data were statistically tested using students t-test, MannWhitney U test or Chi square test when appropriate. In case of differences in incidences between the three AKI definitions a MANOVA post hoc analysis with the Least Significance Difference (LSD) of patient groups was performed. SPSS (IBM 2013, version 22) was used.

II. Review

Search

We conducted a sensitive search in PubMed concerning the comparison of RIFLE, AKIN and KDIGO in critically ill patients (see supplements for search terms). Only studies with adult patients that compared incidence proportions using two or more AKI definitions were considered.

Results

I. Cohort study

Patients

The study was performed in a 42-bed critical care department in a tertiary referral hospital with 3561 admissions in 2014. In the study period 1376 patients were admitted with a total of 5734 observation days. 172 patients were readmitted once or more during the study period. A total of 221 readmissions were excluded for further analysis (figure 1).

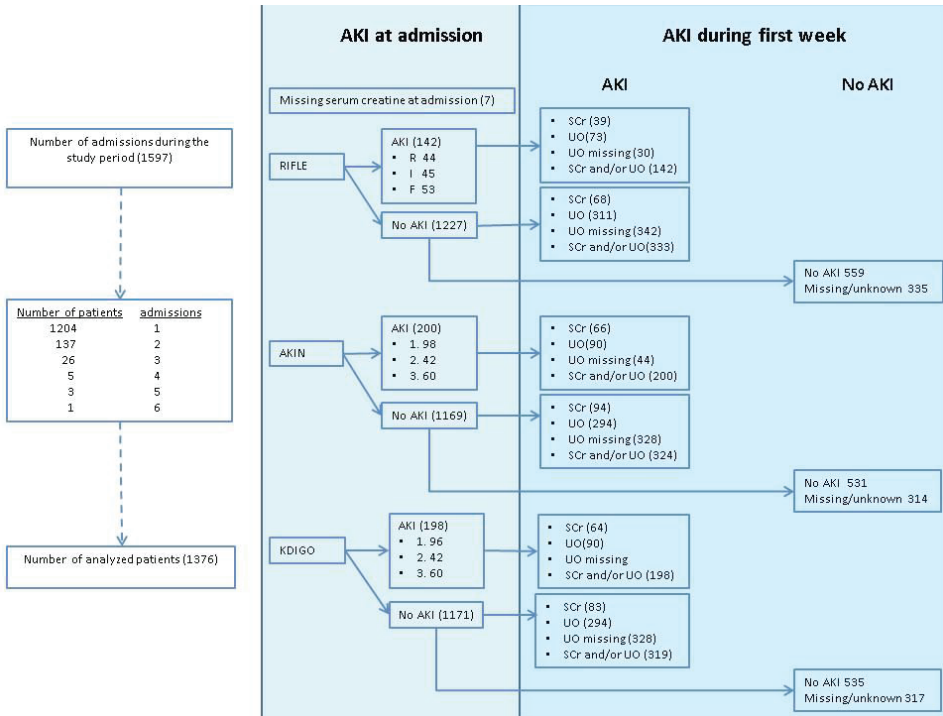


Figure 1. Flowchart with numbers of patients included in the study with AKI at admission and AKI during the first week of admission according to the RIFLE, AKIN and KDIGO definitions

Left column: patients screened for inclusion. Middle column: patients with AKI at admission according to the three definitions and severity. Right column: numbers of patients with AKI during the first week of ICU admission according to the three definitions, severity and with or without urine output criteria. Grouped by patients with AKI at admission and patients without AKI at admission;

RIFLE: 'risk', 'injury', 'failure', 'loss' and 'end-stage' definition

AKIN: acute kidney injury network definition

KDIGO: kidney disease improving global outcome definition

SCr= serum creatinine, UO= urine output

The mean age was 60 years and 63% of patients were male. A surgical intervention preceded admission in 66% of the patients of which 80% were planned. A total of 221 patients (16%) had diabetes and 58 patients (4.2%) had chronic kidney disease (CKD) including 24 patients (1.7%) on chronic renal replacement therapy (RRT). ICU mortality was 5.6% and the median length of ICU stay was 2 days (IQR 2-3) (table 1).

Table 1. Basic patient characteristics

| Characteristic of patients (N=1376) | |
|---|-------------|
| Age (years; mean (sd)) | 60 (16) |
| Male sex (N (%)) | 864 (62.8) |
| Body Mass Index (kg/m ² , mean (sd)) | 26 (5.2) |
| APACHE IV (mean(sd)) | 52 (25) |
| Admission type | |
| • Medical (N (%)) | 461 (33.5) |
| • Surgical (N (%)) | 914 (66.4) |
| ○ scheduled (N (%)) | 727 (52.8) |
| ○ emergency (N (%)) | 187 (13.6) |
| Co morbidity | |
| • diabetes mellitus (N (%)) | 221 (16.1) |
| • chronic kidney disease (N (%)) | 58 (4.2) |
| • chronic dialysis (N (%)) | 24 (1.7) |
| ICU LoS (days; median [IQR]) | 2 [2.0-3.0] |
| ICU mortality (N (%)) | 77 (5.6) |
| Hospital mortality (N (%)) | 129 (9.4) |
| Serum creatinine at admission (μmol/l; median [IQR]) (N=1369) | 73 [58-93] |
| Acute kidney injury in first 7 days of admission | |
| • RIFLE (N (%)) | 210 (15.2) |
| ○ With UO criteria (N (%)) | 475 (34.5) |
| • AKIN (N (%)) | 294 (21.4) |
| ○ With UO criteria (N (%)) | 524 (38.1) |
| • KDIGO (N (%)) | 281 (20.4) |
| ○ With UO criteria (N (%)) | 517 (37.6) |
| • Urine output RIFLE (N (%)) | 265 (19.3) |
| • Urine output AKIN (N (%)) | 230 (16.7) |
| • Urine output RIFLE (N (%)) | 236 (17.2) |
| Renal replacement therapy (N (%)) | 62 (4.5) |

IQR: interquartile range

N: number of patients

APACHE IV: Acute Physiology and Chronic Health Evaluation IV ICU: intensive care unit

LoS: length of stay

UO: urine output

Total prevalence of AKI varies with the definition

A total of 107 patients (7.8%) met the criteria for AKI using the RIFLE definition based on serum creatinine and 384 patients (28%) met the criteria based on urine output during the first week of ICU admission. The combination of serum creatinine and urine output using the RIFLE definition resulted in 475 patients (35%) with AKI. For AKIN 160 patients (12%) met the criteria for AKI based on serum creatinine and 384 patients (28%) met the criteria based on urine output during the first week of ICU admission. The combination of serum creatinine and urine output using the AKIN definition resulted in 524 patients (38%) with AKI. Using the KDIGO definition 147 patients (11%) met the criteria for AKI based on serum creatinine and 384 patients (28%) met the criteria based on urine output during the first week of admission. The combination of serum creatinine and urine output using the KDIGO definition resulted in 517 patients (38%) with AKI (table 1, figure 1 and supplementary table 2).

The patients only fulfilling AKI definitions based on urine output criteria more frequently had diabetes mellitus and were predominantly admitted after scheduled surgery compared to patients who fulfilled AKI criteria based on their serum creatinine (table 2).

Table 2. Patient characteristics and outcome of patients grouped by AKI definition and on positive urine output criteria alone or with serum creatinine criteria

| Definition | RIFLE (N=326) | | | AKIN (N=310) | | | KDIGO (N=308) | |
|------------------------------------|-----------------|-------------------|---------|-----------------|-------------------|---------|-----------------|-------------------|
| | UO only (N=265) | UO and SCr (N=61) | p-value | UO only (N=230) | UO and SCr (N=80) | p-value | UO only (N=236) | UO and SCr (N=72) |
| Characteristics of patients | | | | | | | | p-value |
| Age (years; mean (sd)) | 62 (15) | 63 (15) | 0.753 | 62 (15) | 62 (15) | 0.978 | 62 (15) | 63 (14) |
| Male sex (N (%)) | 173 (54) | 34 (10) | 0.185 | 149 (48) | 45 (15) | 0.182 | 153 (50) | 41 (13) |
| Body Mass Index (kg/m2; mean (sd)) | 27 (5) | 26 (6) | 0.184 | 27 (5.2) | 26 (5.7) | 0.051 | 27 (5.3) | 26 (5.8) |
| APACHE IV score (mean (sd)) | 54 (25) | 75 (22) | 0.000 | 52 (23) | 72 (26) | 0.000 | 52 (23) | 74 (26) |
| Admission type | | | 0.009 | | | 0.052 | | 0.006 |
| • Medical (N (%)) | 105 (32) | 22 (6.7) | | 88 (28) | 31 (10) | | 95 (31) | 22 (7.1) |
| • Surgical | | | | | | | | |
| ○ scheduled (N (%)) | 124 (38) | 21 (6.4) | | 112 (36) | 30 (9.7) | | 112 (36) | 30 (9.7) |
| ○ emergency (N (%)) | 36 (11) | 18 (5.5) | | 30 (9.7) | 19 (6.1) | | 29 (9.4) | 20 (6.5) |

| | | | | | | | | | | | |
|---|----------|----------|-------|----------|----------|-------|----------|-----------|-------|--|--|
| Co morbidity | | | | | | | | | | | |
| <ul style="list-style-type: none">• diabetes mellitus (N (%))• chronic kidney disease (N (%))• chronic dialysis (N (%)) | 47 (14) | 11 (3.4) | 1 | 40 (13) | 12 (3.9) | 0.729 | 41 (13) | 11 (3.6) | 0.857 | | |
| | 3 (0.9) | 2 (0.6) | 0.236 | 2 (0.6) | 3 (0.9) | 0.110 | 2 (0.6) | 3 (0.97) | 0.085 | | |
| | 0 (0) | 0 (0) | na | 0 (0) | 0 (0) | na | 0 (0) | 0 (0) | na | | |
| ICU Length of stay (days; median [IQR]) | | | | | | | | | | | |
| | 3 [2-6] | 6 [3-11] | 0.000 | 3 [2-5] | 6 [3-11] | 0.000 | 3 [2-6] | 5 [3-9.8] | 0.000 | | |
| ICU mortality (N (%)) | | | | | | | | | | | |
| | 13 (4.0) | 6 (1.8) | 0.139 | 8 (2.6) | 11 (3.5) | 0.002 | 10 (3.2) | 9 (2.9) | 0.021 | | |
| Hospital mortality (N (%)) | | | | | | | | | | | |
| | 24 (7.4) | 13 (4.0) | 0.012 | 17 (5.5) | 19 (6.1) | 0.000 | 19 (6.2) | 17 (5.5) | 0.001 | | |

RIFLE: 'risk', 'injury', 'failure', 'loss' and 'end-stage' definition.

AKIN: acute kidney injury network definition

KDIGO: kidney disease improving global outcome definition.

UO: urine output. SCr: serum creatinine

N = number of patients

P-value: difference between patients with only urine output criteria positive and patients with both criteria positive

Table 3. Patient characteristics and outcome of patients grouped by the definition used to classify AKI by serum creatinine criteria

| Characteristic of patients | Group 1 No AKI N=1078 | Group 2 RIFLE, AKIN & KDIGO AKI N=212 | Group 3 AKIN & KDIGO AKI N=70 | Group 4 AKIN AKI N=14 | p value |
|---|---------------------------------|--|---|---------------------------------|--------------|
| Age (years; mean (sd)) | 63 (19) | 67 (20) | 68 (15) | 54 (28) | <0.05 (*) |
| Male sex (N (%)) | 681 (63.1) | 122 (57.5) | 52 (74.3) | 8 (57.1) | 0.078 |
| Body Mass Index (kg/m ² ; mean (sd)) | 25.8 (5.6) | 26.2 (5.6) | 26 (6.2) | 25.6 (4.7) | 0.013 (****) |
| APACHE IV score (mean (sd)) | 43 (25) | 76 (30) | 56 (26.5) | 51.5 (36.5) | 0.001 (***) |
| Admission type | | | | | 0.001 |
| • Medical (N (%)) | 308 (28.6) | 114 (53.8) | 26 (37.1) | 12 (85.7) | |
| • Surgical | | | | | |
| ◦ Scheduled (N (%)) | 640 (59.4) | 53 (25) | 32 (45.7) | 2 (14.3) | |
| ◦ Emergency (N (%)) | 129 (12) | 45 (21.2) | 12 (17.1) | 0 (0) | |
| Co morbidity | | | | | |
| • diabetes mellitus (N (%)) | 149 (13.8) | 62 (29.2) | 9 (12.9) | 1 (7.1) | 0.001 |
| • chronic kidney disease (N (%)) | 5 (0.5) | 48 (22.6) | 4 (5.7) | 0 (0) | 0.001 |
| • chronic dialysis (N (%)) | 0 (0) | 23 (10.8) | 1 (1.4) | 0 (0) | 0.001 |
| ICU Length of stay (days; median [IQR]) | 2 (2-3) | 4 (2-8) | 2 (2-4) | 13 (4-13) | 0.001 (****) |
| ICU mortality (N (%)) | 37 (3.4) | 30 (14.1) | 7 (10) | 3 (21.4) | 0.001 |
| Hospital mortality (N (%)) | 64 (5.9) | 51 (24.1) | 11 (15.7) | 3 (21.4) | 0.001 |

Group 1: patients without AKI, Group 2: patients with AKI according to RIFLE, AKIN and KDIGO criteria, Group 3: patients with AKI according to AKIN and KDIGO, Group 4: patients with AKI according to AKIN

IQR: interquartile range, N: number of patients, APACHE IV: Acute Physiology and Chronic Health Evaluation IV ICU: intensive care unit, LoS: length of stay

(*) group 1 vs group 2 and 3, group 2 vs group 1 and 4, group 3 vs group 1 and 4, (**) group 1 vs group 2, (***) group 2 vs group 1, 3 en 4, group 3 vs group 1 & 2, (****) group 1 vs group 2 and 4, group 3 vs group 1 and 2, group 4 vs group 1, 2 and 3

Eighty-four patients were detected on admission as having AKI using the serum creatinine criteria of the AKIN and KDIGO definitions who remained undetected using the RIFLE definition. Fourteen patients were recognized as having AKI only when using the AKIN definition (table 3). One patient was detected as having AKI only with the KDIGO definition. (not included in table 3). These patients differed in age, severity of illness, admission type, comorbidity, ICU length of stay and mortality. Patients only detected by AKIN and KDIGO were less ill and were admitted more frequently after scheduled surgery compared to the other groups (table 3).

Incidence of AKI varies with the definition

Of all patients who had AKI during the first week of ICU admission 142 patients (10%) were admitted with AKI according to the RIFLE definition, 200 patients (15%) according to the AKIN definition and 198 patients (14%) according to the KDIGO definition (figure 1). Of all patients without AKI according to the RIFLE definition at ICU entry 68 patients (4.9%) developed AKI based on RIFLE serum creatinine criteria. When the AKIN definition was used 94 patients (6.8%) developed AKI and when the KDIGO definition was used 83 patients (6.0%) developed AKI (figure 1 and supplementary table 2).

The severity of AKI during the first week of ICU admission varied with the definitions used

RIFLE stage 'risk' occurred in 67 patients (4.9%) using the creatinine criteria solely and in 230 patients (17%) when combined with the urine output criteria. For RIFLE stage 'injury' this was 62 patients (4.5%) and 144 patients (10%), respectively, and for RIFLE stage 'failure' 81 patients (5.9%) and 86 patients (6.3%), respectively.

Incidence of AKIN stage 1 occurred in 137 patients (10%) based on the creatinine criteria and in 272 patients (20%) when combined with the urine output criteria. For AKIN stage 2 this was 60 patients (4.4%) and 126 patients (9.2%), respectively, and for AKIN stage 3 this was 97 patients (7.0%) and 108 patients (7.9%), respectively.

KDIGO stage 1 occurred in 127 patients (9.2%) based on the creatinine criteria and in 271 patients (20%) when combined with the urine output criteria. For KDIGO stage 2 this was 50 patients (3.6%) and 119 patients (8.6%), respectively, and for KDIGO stage 3 this was 104 patients (7.6%) and 106 patients (7.7%) respectively (supplementary table 2).

Timing of detection of AKI varying with definitions

For urine output criteria, the median time until detection was 13 hours with all three definitions (RIFLE IQR 7-22 hours, AKIN IQR 7-23 hours, KDIGO IQR 7-23 hours). Timing and incidence of AKI based on serum creatinine criteria is comparable between RIFLE, AKIN and KDIGO in the first 48 hours of admission (supplementary figure 1). AKI was detected after a median of 24 hours (IQR 24-48) using the serum creatinine criteria for RIFLE, AKIN or KDIGO definitions (figure 2).

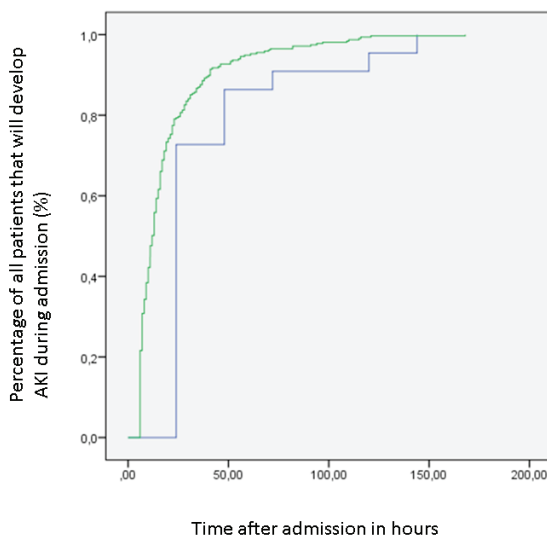


Figure 2. Proportions of patients who develop AKI according to RIFLE definition during ICU admission

Proportions of patients who develop AKI according to RIFLE definitions based on urine output criteria (green line) and serum creatinine criteria (blue line) plotted against the time in hours since admission to the ICU. Only patients without AKI at ICU admission who developed AKI within the first week of ICU admission are included in this graph.

II. Review

A total of 383 hits were screened and 24 papers that compared RIFLE, AKIN and/or KDIGO definitions were selected for inclusion (supplementary table 3). One study was published as abstract only [19]. Fourteen studies evaluated incidences of AKI in critically ill patients and found proportions varying from 34% to 81% using RIFLE definition, from 29% to 77% using AKIN definition and from 38% to 51% using KDIGO definition.

AKI incidences in critically ill patients in prospective studies

Six studies used a prospective design to evaluate AKI incidences based on two or more definitions. Two studies compared all three AKI definitions RIFLE, AKIN and KDIGO and two other studies compared two AKI definitions. All studies excluded specific subgroups from their studies when defining AKI incidences. Three studies used urine output criteria in addition to creatinine for defining AKI.

Luo et al., evaluated AKI based on RIFLE, AKIN and KDIGO in 3107 patients. This study excluded patients who stayed in the ICU for less than 24 hours and patients with end stage kidney disease, patients on RRT and patients who had a renal transplant in the preceding 3 months. Baseline creatinine was based on the lowest creatinine in the preceding 3 months, or the ideal creatinine based on $75 \text{ ml/min/1.73m}^2$ using the MDRD, or the lowest creatinine during ICU admission. AKI severity was based on the highest classification using both serum creatinine and urine output criteria, measured either hourly or averaged over 6 hours. AKI incidences were 47%, 38%, and 51% using RIFLE, AKIN, and KDIGO definitions, respectively [20].

The study of Levi et al., compared all three definitions in 190 patients and excluded patients admitted for less than 24 hours and patients on RRT before admission. The authors did not specify baseline creatinine and used average urine output over 6 hours. AKI incidences were 63% for all three definitions. The distribution of AKI severity differed between AKIN and KDIGO in stages 2 and 3 [21].

Reddy et al., compared AKI incidences using RIFLE and AKIN definitions in 250 patients. All patients with a preexisting renal disease were excluded. Baseline creatinine was based on the lowest serum creatinine during hospital or ICU admission or calculated based on a MDRD of $75 \text{ ml/min/1.73m}^2$. AKI was based on both creatinine and urine output criteria, but measurement of urine output collection was not specified. The authors found higher incidences of AKI using AKIN compared to RIFLE (46% versus 34%) [22].

Wlodzimierow et al., compared incidences in AKI based on RIFLE in 260 ICU patients admitted for at least 48 hours and excluded patients with known end stage renal disease. The lowest value of serum creatinine in the preceding 6 months or the estimated serum creatinine based on the MDRD assuming a clearance of $75 \text{ ml/min/1.73m}^2$ was used as reference value. Urine output was measured hourly. Incidences of AKI with and without urine output criteria were 81% and 42%, respectively [15].

Macedo et al., compared incidence in AKI based on AKIN in 75 patients and excluded patients with known end stage renal disease or receiving RRT. The first serum creatinine at ICU admission was used as reference creatinine and urine output was measured hourly. The incidences of AKI according to the AKIN definitions were 28%, 55% and 60% based on serum creatinine, urine output, and a combination, respectively [16].

A multicenter study by Salgado et al., in 627 ICU patients compared AKI incidences using RIFLE and AKIN definitions with and without urine output criteria in patients admitted for at least 48 hours. They excluded patients in whom urine output was not possible to quantify, patients with previous urological interventions or patients on RRT. Missing urine output data were estimated using calculating averages. AKI incidences were 69% and 52% using RIFLE and AKIN definitions, with similar AKI incidences when adding urine output criteria (60% with both definitions) [17].

AKI incidences in critically ill patients in retrospective studies

Eight studies used a retrospective design to evaluate AKI incidences. No study compared all three definitions. Seven studies compared two definitions and one evaluated the additive value of urine output on AKI incidences. Two studies found AKI incidences of 36% using RIFLE definitions and 26% and 37% using AKIN definitions [23, 24]. Four other studies found AKI incidences in patients with sepsis varying from 56% to 68% depending on the definitions used [25-28]. All studies used serum creatinine and four studies also used urine output criteria. A MDRD of 75 ml/min/1.73m² was used as a reference value for serum creatinine in four studies, and in three studies the lowest serum creatinine was used. Urine output was measured as an average over 24 hours in one study and not further specified in three studies. One study analyzed the additional value of urine output in AKIN definitions and found that 12% remained unrecognized as having AKI based on serum creatinine [14, 18].

AKI incidences in other populations

Ten studies assessed patients that were not critically ill of which four had a prospective and six a retrospective design. Three studies with a prospective and three with a retrospective design compared all three AKI definitions. Incidences varied from 4-94%. None of the studies evaluated the additional value of urine output criteria.

Discussion

We have analyzed differences in AKI incidences based on the three available definitions of RIFLE, AKIN, and KDIGO, each with and without urine output criteria. Urine output criteria increase AKI proportions using all three definitions by adding less sick patients but also enable quicker recognition of AKI by half a day. While RIFLE criteria were initially developed for uniform and standardized reporting of outcomes, our review shows that reported AKI incidences are far from uniform.

The RIFLE AKI definition was developed for lack of clear definitions of AKI and to facilitate uniform reporting renal failure. All AKI definitions, however are validated against mortality because a gold standard for AKI is absent. In fact, AKI criteria are prognostic factors for mortality based on renal symptoms, but the performance as prognostic score for mortality is mediocre [1]. Fulfilling RIFLE creatinine definition requires a higher (at least 50%) creatinine rise than the absolute criterion of 26.4 µmol/l for the AKIN and KDIGO definitions and patients will meet AKIN and KDIGO criteria more easily (figure 1 and supplementary figure 1). Patients who meet RIFLE definition will therefore be sicker as reflected by the APACHE score and have a higher mortality (table 3). Introduction of a fixed rise in creatinine improves sensitivity but occurs at the cost of specificity.

Adding urine output also leads to a shift in the features of the patients identified to have AKI. A decreased urine output may be the first signal of renal function loss but only 20% will reach the AKI serum creatinine criteria (figure 1 and supplementary table 2). Patients only fulfilling urinary output criteria have a lower APACHE IV score (table 2). Urine output is frequently not reported in

publications for practical reasons. Our data show that AKI incidences will rise considerably when urine output criteria are included while patient outcome probably improves (table 2) which is corroborated by a recent study [14].

Our overall AKI incidence of 15% when using serum creatinine criteria of the RIFLE definition or 38% when using the combination of serum creatinine and urine output criteria of the AKIN and KDIGO definitions are relatively low compared to the literature.

This could be explained by not having any exclusion criterion in our study, as we included patients with less severe illness. Two third of our patient population was admitted less than 48 hours. These design issues could have diluted the AKI incidences. In contrast, we used baseline serum creatinine based on an ideal creatinine using a MDRD of 75 ml/min/1.73m² which could have led to overestimation of true incidences as we scored some patients with - previously unknown - CKD as having AKI. The choice which baseline serum creatinine is used has an important effect on incidence of AKI and subsequent on mortality in patients with AKI (29). However, using an estimated creatinine is widely accepted in studies on AKI for determining baseline creatinine [30]. It is debatable whether these patients have substantial impact on our results as our population contains only 4.2% patients with known CKD. We had only urine output data in 1004 patients which could lead to both over and underestimation of AKI incidences. A possible limitation in our urine output data is the fact that imputation was based on averages using the first known value over the missing hours. Unlike the study of Soliman et al, we did not restrict our backlogging process to 6 hours, which could induce possible overestimation of AKI based on the urine output criteria [31].

The considerations mentioned above are applicable to most studies concerning incidence of AKI in critically ill patients. Our presented literature review showed large heterogeneity in patients included, AKI definition used, reference or baseline serum creatinine used, timeframe in which AKI was assessed and whether urine output was used. This inclusion, definition and reference creatinine heterogeneity could explain the differences in AKI incidence in these studies and makes published studies difficult to compare. We intended to conduct a sensitive literature search. However, a sensitive search strategy is always a trade-off between a sufficiently large numbers of hits so that it can be considered sensitive and a sufficiently low numbers of hits so that it can be achievable. With different search criteria other studies might also have been included.

More than a third of patients who only fulfilled AKI criteria based on urine output were admitted after scheduled surgery (table 2). The significance of oliguria only in the post-operative period is relatively unknown and it is questionable if the prognostic value of AKI diagnosis and classification on oliguria only is applicable to these patients, although patients only fulfilling urine output criteria have higher one year mortality than patients not meeting one of the AKI criteria [14, 32, 33]. The addition of urine output criteria to serum creatinine criteria leads to higher AKI incidences with earlier recognition especially in patients with mild to moderate AKI. It may be possible that more frequent measurements of serum creatinine also reduce the time needed for AKI detection but

that would increase costs. Earlier recognition of patients having AKI could provide possibilities for prevention of kidney function deterioration and potentially improve outcomes [34]. Furthermore, especially long-term follow up data are needed to evaluate associations between AKI based on urine output criteria only and kidney function and survival.

Conclusion

AKIN and KDIGO define a less ill population with a better outcome, compared to RIFLE. Urine output criteria detect patients with AKI 11 hours earlier than serum creatinine criteria and gives approximately doubling of AKI incidences in critically ill patients, but most of these patients will never reach creatinine criteria. Consensus definitions have improved research opportunities, however the definitions used, addition of urine output criteria and the patients under study all influence AKI incidences and possibly outcomes.

List of abbreviations

| | |
|--------|--|
| AKI | acute kidney injury |
| AKIN | Acute Kidney Injury Network |
| APACHE | Acute Physiology and Chronic Health Evaluation IV |
| BMI | Body Mass Index |
| CKD | Chronic Kidney Disease |
| GFR | Glomerular Filtration Rate |
| ICU | Intensive Care Unit |
| IQR | Inter Quartile Range |
| KDIGO | Kidney Disease Improving Global Outcome |
| METc | Medisch Ethische Toetsings commissie (<i>Medical Ethics Committee</i>) |
| MDRD | Modification of Diet in Renal Disease |
| RIFLE | Risk, Injury, Failure |
| RRT | Renal Replacement Therapy |

Declarations

Ethics

Informed consent was waived by the institutional Review Board of the University Medical Center Groningen because the study had an observational design and all data were de-identified (METc 2013-174).

Consent to publish

Not applicable.

Competing interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Author' contributions

Conceived and designed the study and analysis: JK, EK, IH, JZ and MM. Analyzed the data: JK and EK. Contributed to gathering the data: WD. Wrote the paper: JK, EK, IH, JZ and MM.

Availability of data and materials

On request.

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Chapter2

SUPPLEMENTARY MATERIAL

Supplementary methods

I. Cohort study

Definitions of AKI

RIFLE definition: RIFLE definition for AKI has five stages of kidney dysfunction. Risk is defined by a rise in serum creatinine of 50% from baseline, a decline in glomerular filtration rate (GFR) of 25% or more compared to baseline or a urine output less than 0.5 ml/kg/h during at least 6 hours. Injury is defined by a doubling of serum creatinine from baseline, a decline in GFR of 50% or more compared to baseline or a urine output less than 0.5 ml/kg/h during at least 12 hours. Failure is defined by an increase of serum creatinine with 300% from baseline, an acute rise in serum creatinine of $\geq 44 \mu\text{mol/l}$ from baseline, a serum creatinine of $\geq 350 \mu\text{mol/l}$, a decline in GFR of 75% compared to baseline, a urine output less than 0.3 ml/kg/h during 24 hours or anuria during at least 12 hours. Loss is defined by persistent loss of kidney function during at least 4 weeks and End Stage Kidney Disease is defined by persistent loss of kidney function during at least 3 months. Loss and End Stage Kidney disease were not used in this study [1]. The time span during which the rise in serum creatinine should occur was not mentioned in the original publication by Bellomo, but was defined 7 days by Kellum [2].

AKIN definition: AKIN definition for AKI has three stages of kidney function. Stage 1 is defined by a rise in serum creatinine of at least $26.4 \mu\text{mol/l}$, a rise in serum creatinine of 150-200% from baseline or urine output less than 0.5 ml/kg/h for more than 6 hours. Stage 2 is defined by a rise in serum creatinine of 200-300% from baseline or urine output less than 0.5 ml/kg/h during more than 12 hours. Stage 3 is defined by a rise in serum creatinine of more than 300% from baseline, a serum creatinine $\geq 354 \mu\text{mol/l}$ with an acute increase of at least $44 \mu\text{mol/l}$, the need for RRT or a urine output less than 0.3 ml/kg/h during 24 hours or anuria during 12 hours. The rise in serum creatinine has to occur within 48 hours [3].

KDIGO definition: KDIGO definition for AKI has three stages of kidney function. Stage 1 is defined by a 1.5-1.9 fold rise in serum creatinine within 7 days compared to baseline, an absolute rise of $\geq 26.5 \mu\text{mol/l}$ within 48 hours compared with baseline or a urine output of less than 0.5 ml/kg/h during 6 to 12 hours. Stage 2 is defined by a 2.0-2.9 fold rise in serum creatinine within 7 days compared with baseline or a urine output less than 0.5 ml/kg/h during at least 12 hours. Stage 3 is defined by a 3 fold rise in serum creatinine within 7 days compared with baseline, an absolute serum creatinine $\geq 354.6 \mu\text{mol/l}$, initiation of renal replacement therapy (RRT), a urine output less than 0.3 ml/kg/h during at least 24 hours or anuria during more than 12 hours [4]. The different AKI definitions are summarized in supplementary table 1.

Supplementary table 1. RIFLE, AKIN and KDIGO definitions with serum creatinine and urine output criteria

| | RIFLE | AKIN | KDIGO | RIFLE, AKIN & KDIGO |
|----------------------|--|--|---|---|
| Serum creatinine | Urine output | | | |
| 1 or Risk | creatinine *1.5 Or GFR decrease >25% | creatinine + ≥ 26.4 μmol/l Or creatinine 150-200% (*1.5-2.0) | creatinine *1.5-1.9 Or creatinine + ≥ 0.3 mg/dl (26.5 μmol/l) | <0.5 ml/kg/h ≥ 6u |
| 2 or Injury | creatinine *2 Or GFR decrease >50% | creatinine 200-300% (*>2.0-3.0) | creatinine * 2.0-2.9 | <0.5 ml/kg/h ≥ 12u |
| 3 or Failure | creatinine *3 Or creatinine ≥ 4 mg/dl (350 μmol/l) with acute increase ≥ 0.5 (44 μmol/l) mg/dl Or GFR decrease 75% | creatinine >300% (*>3.0) Or creatinine ≥ 4 mg/dl (354 μmol/l) with acute increase ≥ 0.5 mg/dl (44 μmol/l) Or RRT | creatinine *3 Or creatinine ≥ 4 mg/dl (354 μmol/l) Or RRT | < 0.3 ml/kg/h ≥ 24u Or Anuria ≥ 12u |
| Time interval | < 1-7 days | < 48 hours | < 7 days | |

RIFLE: 'risk', 'injury', 'failure', 'loss' and 'end-stage' definition

AKIN: acute kidney injury network definition

KDIGO: kidney disease improving global outcome definition

GFR: glomerular filtration rate

UO: urine output

II. Review

Search terms

RIFLE vs AKIN vs KDIGO

((AKIN[All Fields] OR ("acute kidney injury"[MeSH Terms] OR ("acute"[All Fields] AND "kidney"[All Fields] AND "injury"[All Fields]) OR "acute kidney injury"[All Fields])))

AND

((("rifl"[All Fields]) OR (("risk"[MeSH Terms] OR "risk"[All Fields]) AND "injury"[All Fields] AND failure[All Fields] AND loss[All Fields] AND end[All Fields] AND stage[All Fields]))

AND

(kdigo[All Fields] OR (("kidney diseases"[MeSH Terms] OR ("kidney"[All Fields] AND "diseases"[All Fields]) OR "kidney diseases"[All Fields] OR ("kidney"[All Fields] AND "disease"[All Fields]) OR "kidney disease"[All Fields]) AND improving[All Fields] AND ("global"[All Fields]) AND outcomes[All Fields]))

RIFLE vs AKIN

((AKIN[TiAb] OR ("acute kidney injury"[MeSH Terms] OR ("acute"[TiAb] AND "kidney"[TiAb] AND "injury"[TiAb]) OR "acute kidney injury"[TiAb]))) AND ((("rifle"[TiAb]) OR (("risk"[MeSH Terms] OR "risk"[TiAb]) AND "injury"[TiAb] AND failure[TiAb] AND loss[TiAb] AND end[TiAb] AND stage[TiAb])) AND ((("critical care"[MeSH Terms] OR ("critical"[TiAb] AND "care"[TiAb]) OR "critical care"[TiAb]) OR ("intensive care"[MeSH Terms] OR ("intensive"[TiAb] AND "care"[TiAb]) OR "intensive care"[TiAb]) OR ICU[TiAb] OR ("critical illness"[MeSH Terms] OR ("critical"[TiAb] AND "illness"[TiAb]) OR "critical illness"[TiAb] OR ("critically"[TiAb] AND "ill"[TiAb]) OR "critically ill"[TiAb]))

RIFLE vs KDIGO

((("rifle"[TiAb]) OR (("risk"[MeSH Terms] OR "risk"[TiAb]) AND "injury"[TiAb] AND failure[TiAb] AND loss[TiAb] AND end[TiAb] AND stage[TiAb])) AND (kdigo[TiAb] OR ((("kidney diseases"[MeSH Terms] OR ("kidney"[TiAb] AND "diseases"[TiAb]) OR "kidney diseases"[TiAb] OR ("kidney"[TiAb] AND "disease"[TiAb]) OR "kidney disease"[TiAb]) AND improving[TiAb] AND ("global"[TiAb] AND outcomes[TiAb])) AND ((("critical care"[MeSH Terms] OR ("critical"[TiAb] AND "care"[TiAb]) OR "critical care"[TiAb]) OR ("intensive care"[MeSH Terms] OR ("intensive"[TiAb] AND "care"[TiAb]) OR "intensive care"[TiAb]) OR ICU[TiAb] OR ("critical illness"[MeSH Terms] OR ("critical"[TiAb] AND "illness"[TiAb]) OR "critical illness"[TiAb] OR ("critically"[TiAb] AND "ill"[TiAb]) OR "critically ill"[TiAb]))

AKIN vs KDIGO

((AKIN[TiAb] OR ("acute kidney injury"[MeSH Terms] OR ("acute"[TiAb] AND "kidney"[TiAb] AND "injury"[TiAb]) OR "acute kidney injury"[TiAb]))) AND (kdigo[TiAb] OR ((("kidney diseases"[MeSH Terms] OR ("kidney"[TiAb] AND "diseases"[TiAb]) OR "kidney diseases"[TiAb] OR ("kidney"[TiAb] AND "disease"[TiAb]) OR "kidney disease"[TiAb]) AND improving[TiAb] AND ("global"[TiAb] AND outcomes[TiAb])) AND ((("critical care"[MeSH Terms] OR ("critical"[TiAb] AND "care"[TiAb]) OR "critical care"[TiAb]) OR ("intensive care"[MeSH Terms] OR ("intensive"[TiAb] AND "care"[TiAb]) OR "intensive care"[TiAb]) OR ICU[TiAb] OR ("critical illness"[MeSH Terms] OR ("critical"[TiAb] AND "illness"[TiAb]) OR "critical illness"[TiAb] OR ("critically"[TiAb] AND "ill"[TiAb]) OR "critically ill"[TiAb]))

Supplementary results

Supplementary table 2. Severity of AKI during first week grouped by patients with AKI at admission and those who developed AKI during the first week of ICU admission by RIFLE, AKIN and KDIGO definition based on serum creatinine and urine output criteria

| | | AKI at admission | | | | | No AKI at admission | | | | | All patients |
|--------------|--------------|------------------|-----|-----|---------|-------|---------------------|-----|-----|--------|---------|--------------|
| | | UO criteria | | | | Total | UO criteria | | | | | |
| | | R/1 | I/2 | F/3 | Missing | | R/1 | I/2 | F/3 | No AKI | Missing | Total |
| Scr criteria | RIFLE | | | | | | | | | | | |
| | Risk | 3 | 7 | 1 | 14 | 25 | 7 | 14 | 4 | 17 | | 42 |
| | Injury | 5 | 8 | 1 | 28 | 42 | 3 | 6 | 7 | 4 | | 20 |
| | Failure | 10 | 20 | 18 | 27 | 75 | 1 | 2 | 2 | 1 | | 6 |
| | No AKI | 0 | 0 | 0 | 0 | 0 | 170 | 88 | 7 | 559 | 335 | 1159 |
| | Total | 18 | 35 | 20 | 69 | 142 | 181 | 110 | 20 | 581 | 335 | 1227 |
| | | | | | | | | | | | | |
| Scr criteria | AKIN | | | | | | | | | | | |
| | 1 | 8 | 15 | 0 | 52 | 75 | 18 | 18 | 1 | 25 | | 62 |
| | 2 | 5 | 9 | 2 | 25 | 41 | 5 | 7 | 6 | 1 | | 19 |
| | 3 | 10 | 20 | 33 | 21 | 84 | 0 | 3 | 6 | 4 | | 13 |
| | No AKI | | | | | | 153 | 73 | 4 | 531 | 314 | 1075 |
| | Total | 23 | 44 | 23 | 110 | 200 | 176 | 101 | 17 | 561 | 314 | 1169 |
| | | | | | | | | | | | | |
| Scr criteria | KDIGO | | | | | | | | | | | |
| | 1 | 8 | 15 | 0 | 49 | 72 | 14 | 19 | 2 | 20 | | 55 |
| | 2 | 5 | 6 | 1 | 26 | 38 | 3 | 5 | 3 | 1 | | 12 |
| | 3 | 10 | 23 | 22 | 33 | 88 | 1 | 3 | 8 | 4 | | 16 |
| | No AKI | | | | | | 158 | 74 | 4 | 535 | 317 | 1088 |
| | Total | 23 | 44 | 23 | 108 | 198 | 176 | 101 | 17 | 560 | 317 | 1171 |
| | | | | | | | | | | | | 1369 |

Left: patients with AKI at admission. Right: patients without AKI at admission. Numbers of patients with AKI according to serum creatinine and urine output grouped by severity and AKI definition.

Supplementary table 3. Studies used in the review

| Study | N | Baseline creatinine | UO criteria and method | Exclusion criteria | Setting | RIFLE | AKIN | KDIGO |
|-------------------------------------|------|---|---|--|---------|-------------|-------------|-----------|
| Prospective studies in ICU patients | | | | | | | | |
| Luo (2014) [5] | 3107 | Lowest SCr in the past 3 months | Hourly or total volume in a 6-hour period | ESKD RRT Kidney transplantation <3 months ICU admission <24 hours | ICU | Total 46.9% | Total 38.4% | Total 51% |
| | | If unknown: RIFLE and KDIGO: estimated (MDRD (75 ml/min/1.73m ²)) (N=120) baseline or lowest SCr during ICU admission (N=634) AKIN: SCr at ICU admission | | | | | | |

| | | | | | | | | |
|---------------------------|-----|--|---|--|-----|--|--|--|
| Salgado (2014) [6] | 627 | MDRD (75 ml/min/1.73m ²) | Average hourly UO based on two-hourly collection by CAD or based on micturition episodes. | Inability to quantify UO at any time during study period Surgical instrumentation of the urinary tract RRT (new onset or chronic) ICU admission <48 hours | ICU | Total: 69.4% <ul style="list-style-type: none"> urine criteria: 59.5% creatinine criteria: 34.7% | Total: 51.8% <ul style="list-style-type: none"> urine criteria: 59.5% creatinine criteria: 25.3% | |
| Reddy (2014) [7] | 250 | Lowest of MDRD (75 ml/min/1.73m ²), during hospital admission or ICU admission | Not stated but used for classification | CCU admission Any known pre-existing renal disease (baseline SCr >1.3 mg/dl men, >1.2 mg/dl women or by decision of consulting nephrologist) | ICU | Risk: 25.3% Injury: 27.7% Failure: 46.9% Total: 34.3% | 1: 44.1% 2: 20.7% 3: 35.2% Total: 45.9% | |

| | | | | | | | | |
|---------------------------------------|------|--|---|--|-----|---|---|---|
| Levi (2013) [8] | 190 | Not stated | UO measured every 6 hours | ICU admission <24 hours RRT before admission | ICU | Risk: 30.5% Injury: 14.7% Failure 17.4% Total: 62.6% | 1: 37.4% 2: 7.9% 3: 17.9% Total: 63.2% | 1: 37.4% 2: 7.4% 3: 18.4% Total: 63.2% |
| Wlodzimirow (2012) [9] | 260 | Lowest of SCr <6 months of ICU admission or MDRD (75 ml/min/1.73m ²) | UO measured hourly | ICU admission < 48 hours Known ESKD RRT before admission | ICU | Risk: 18% Injury: 19% Failure: 3% Total with UO: 81% Total without: 42% | | |
| Macedo (2011) [10] | 75 | First measured SCr at ICU admission | UO measured by a digital continuous urine meter | Known ESKD RRT before admission | ICU | Total: • Creatinine 4/75 • UO 24/75 • Creatinine and/or UO 17/75 | | |
| Retrospective studies in ICU patients | | | | | | | | |
| Shinjo (2014) [11] | 2579 | Lowest SCr during hospitalisation | Not used | Known ESKD RRT before admission Kidney transplant ICU admission < 24 hours | ICU | 1: 20.7% 2: 3.4% 3: 5.4% Total: 29.5% | 1: 24.8% 2: 6.2% 3: 7.5% Total: 38.4% | |

| | | | | | | | | |
|------------------------------|-----|---|----------------------------|---|---|--|--|--|
| Ratanarat (2013) [12] | 300 | Not stated (abstract only) | Not stated (abstract only) | Not stated (abstract only) | ICU | Risk: 12.7% Injury: 20.7% Failure: 33.3% Total: 66.7% | 1: 16% 2: 13.3% 3: 47.3% Total: 76.7% | |
| Kim (2012) [13] | 326 | Lowest SCr <3 months or MDRD (75 ml/min/1.73m2) if unknown (N=61) AKIN: SCr at ICU admission | UO measured hourly | (chronic) RRT before admission ICU admission <24 hours | ICU patient s with severe sepsis/septic shock | Risk (48h): 21.0% Risk (72h): 13.6% Injury (48h): 21.6% Injury (72h): 20.8% Failure (48h): 20.3% Failure (72h): 21.1% Total (48h): 62.9% Total (72h): 55.5% | 1 (48h): 22.8% 1 (72h): 17.0% 2 (48h): 17.9% 2 (72h): 15.1% 3 (48h): 25.1% 3 (72h): 27.2% Total (48h): 65.6% Total (72h): 59.2% | |

| | | | | | | | | |
|-----------------------------|------|---|--------------------------|--|--|--|---|--|
| Han (2012) [14] | 1625 | Lowest SCr <7 days | UO measured hourly | Known CKD Known ESKD | ICU | | 1: Creatinine: 548/1625 UO: 215/1625 2: Creatinine: 100/1625 UO: 113/1625 3: Creatinine: 179/1625 UO: 90/1625 Total: 57% ((1625- 699)/1625) | |
| Chang (2010) [15] | 291 | First SCr during hospitalization or MDRD (75 ml/min/1.73m ²) if admitted directly to the ICU (N=20) | Not stated / used | Chronic uremic patients on RRT Hospital admission <24 hours | ICU patient s with septic shock, ARDS or hepatic cirrhosi s | Risk: 13.1% Injury: 17.9% Failure: 29.9% Total: 60.8% | 1: 19.6% 2: 16.8% 3: 12.3% Total: 68% | |

| | | | | | | | | |
|------------------------------|-------------|---|---|---|-----|---|--|--|
| Joannidis (2009) [16] | 16.7 84 | MDRD (75 ml/min/1.73m ²) | Average UO measured over 24h | Chronic renal failure according to SAPS 3 handbook (a.o. RRT) Kidney transplantation | ICU | Risk: 7.6% Injury: 11.1% Failure: 16.8% Total: 35.5% | 1: 7.5% 2: 7.2% 3: 13.8% Total: 28.5% | |
| Lopes (2008) [17] | 662 | MDRD (75 ml/min/1.73m ²) | UO measured hourly | Chronic kidney disease RRT before admission | ICU | Risk: 14.7% Injury: 11% Failure: 18.1% Total: 43.8% | 1: 21.1% 2: 10.1% 3: 19.2% Total: 50.4% | |
| Bagshaw (2008) [18] | 120. 123 | MDRD (75 ml/min/1.73m ²) | Average UO measured over 24h (patient weight assumed 70kg) | ESKD RRT before admission Kidney transplantation | ICU | Risk: 16.2% Injury: 13.6% Failure: 6.3% Total: 36.1% | 1: 18.1% 2: 10.1% 3: 8.9 Total: 37.1% | |

| Prospective studies in non-ICU patients | | | | | | | |
|---|------|---------------------------------|------------|---|---|--|--|
| Neves (2014) [19] | 69 | Not stated | Not stated | ICU admission < 72h Stage 5 CKD Renal transplantation | Patient s 72h in the interna l ward with AKI or exacer bation of CKD on admissi on or develo ped during hospita lisation | Risk: 26.1% Injury: 23.2% Failure: 45% Total: 94.2% | 1: 29.0% 2: 26.1% 3: 29.0% Total: 84.1% |
| Rodrigues (2013) [20] | 1050 | MDRD (75 ml/min/1.73m2) ? | Not used | Hospital admission < 48h | (N)STE MI | Risk: 9.6% Total: 14.8% | 1: 30.8% Total: 36.6% |

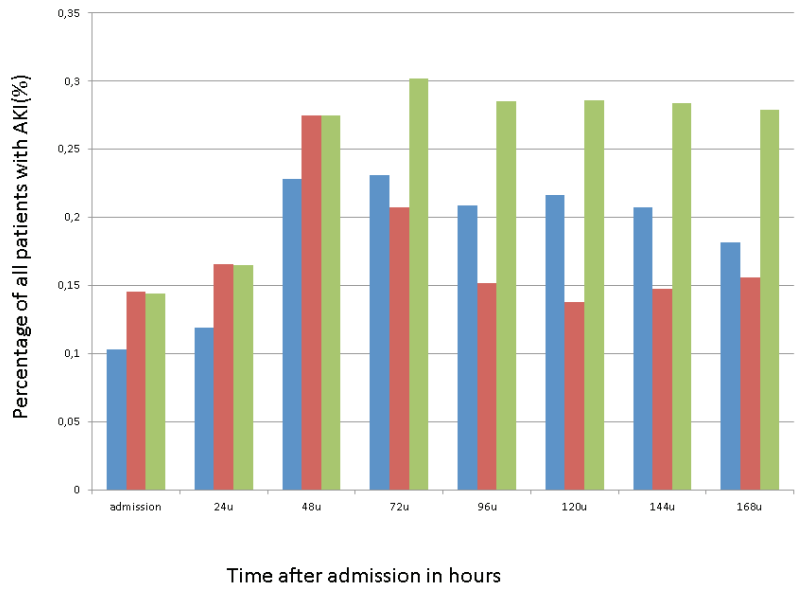
| | | | | | | | | |
|----------------------------|-----|--------------------------|----------|---|---|--------------|--------------|--------------|
| Roy (2013) [21] | 637 | SCr < 1year of admission | Not used | RRT before admission Renal transplantation | Patient s admitt ed with systolic heart failure | Total: 25.6% | Total: 27.9% | Total: 26.5% |
| Sampaio (2013) [22] | 321 | SCr pre-operative | Not used | SCr >= 2.5 mg/dl pre-operative | Patient s admitt ed for myocar dial revasc ularizat ion surgery , valve replace ment or both | Total: 15% | Total: 51% | Total: 19% |

| Retrospective studies in non-ICU patients | | | | | | | |
|---|------------|---|--------------------|---|-----------------------|---|--|
| Karapanagiotou (2014) [23] | 71 | Not stated | UO measured hourly | Liver retransplantation Liver- & kidney transplantation Acute hepatic failure | Liver transplant | Risk: 12.7% Injury: 12.7% Failure 14.1% Total: 39.4% | 1: 22.5% 2: 7% 3: 22.5% Total: 52.1% |
| Fujii (2014) [24] | 49.5 18 | Most recent SCr 1-12 months before admission or based on MDRD (75 ml/min/1.73m ²) | Not used | CKD5 at admission and RRT RRT before admission Hospital admission <2 days | Hospitalized patients | Total: 16.1% | 1: 70.9% 2: 17.1% 3: 12.0% Total: 18.3% |

| | | | | | | | | |
|----------------------------|------|---|----------|--|--|---|---|---|
| Li (2014) [25] | 1005 | Lowest SCr at admission (if in normal range) or SCr < 3 months of admission (27%). MDRD (75 ml/min/1.73m2) if no SCr was available | Not used | No SCr available in first 7 days of hospitalization Hospitalisation <48 hours ESRD with RRT SCr at admission > = 3.5 mg/dl Malignant tumor Cardiac surgery Contrast medium associated AKI | Hospitalized patients with acute heart failure | Risk: 14.0% Injury: 11.5% Failure: 6.6% Total: 32.1% | 1: 15.6% 2: 10.0% 3: 9.1% Total: 34.7% | 1: 19.3% 2: 10.3% 3: 9.3% Total: 38.9% |
| Shacham (2014) [26] | 1033 | SCr at hospital admission | Not used | Admission <24 hours RRT before admission | STEMI | Risk: 1.9% Total: 3.9% | 1: 7.6% Total: 9.6% | |

| | | | | | | | | |
|------------------------------|------|---|--|--|---|--|---|--------------|
| Bastin (2013) [27] | 1922 | Most recent SCr (pre-admission clinic or hospital admission) | Not used | VAD ECMO Cardiac transplantation ≥ 2 CPB episodes in 1 admission RRT before surgery Death <24 hours after surgery | Patient s after cardiac surgery with CPB | Risk: 17.9% Injury: 5.2% Failure: 1.9% Total: 24.9% | 1: 16.9% 2: 1.8% 3: 7.2% Total: 25.9% | Same as AKIN |
| Han (2011) [28] | 120 | SCr at hospital admission | Average UO over 24 hours (patient weight assumed 70kg) | CKD RRT before admission Hypertension DM Admission <24 hours | Hantaav nirus | Risk (48h): 14.2% Risk (1w): 7.5% Injury (48h): 10.8% Injury (1w): 13.3% Failure (48h): 54.2% Failure (1w): 63.3% Total (48h): 79.2% Total (1w): 84.2% | 1 (48h): 17.5% 1 (1w): 12.5% 2 (48h): 10% 2 (1w): 13.3% 3 (48h): 55.0% 3 (1w): 63.3% Total (48h): 82.5% Total (1w): 89.2% | |

Supplementary figure 1. Incidences of AKI during the first week after admission according to the serum creatinine criteria of the RIFLE, AKIN and KDIGO definitions



y-axis: proportions of all patients

x-axis: time (in hours) following admission to the Intensive Care Unit (ICU).

Blue columns: proportion according to RIFLE definition, red columns: proportions according to AKIN definition, green columns: proportions according to KDIGO definition.

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